Peer Review File

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Reviewer Comments

Reviewer A

Comment 1: I do not really understand why the perspective is "translational" as stated in the title. I think it is misleading so please consider changing the title.

Reply 1: Thank you for your comments. The perspective is “translational” because it focuses on the “bench to bedside” process of different localization techniques for non-palpable breast lesions.

Comment 2: It would be helpful if the authors also described intraoperative control mechanisms such as specimen radiography with and without Klinitray, specimen ultrasound, etc.

Reply 2: Additional information has been added in line 138-140

“Lastly, intraoperative imaging can be performed (including specimen mammography, specimen ultrasound) after excision of breast lesion in order to ensure a complete excision, to document the removal of wire or marker, and to assess margin status, which can allow immediate re-excision if needed to. (10)

Lin C, Wang K-y, Chen H-l, Xu Y-h, Pan T, Chen Y-d. Specimen mammography for intraoperative margin assessment in breast-conserving surgery: a meta-analysis. Scientific Reports. 2022;12(1):18440.

Reviewer B

Comment 1: Lane 2: The proposed title ending “…several considerations” is vague. It needs some Good review of available localization techniques in non-palpable breast cancer. Areas of improvement would include data on the comparative effectiveness of the different techniques localization techniques on outcomes such as positive margin, cost-effectiveness, and patient-reported outcomes. New localization efforts such as using augmented reality might be of interest to the readers.

There are a few points that require attention before considering the manuscript for publication.

Clarity of Language:

I believe this is one of the strengths of the review as it clearly describes the selected techniques

Inclusion of Recent Advancements:

I believe that localization with augmented reality techniques should also be mentioned and a description of its advantages and disadvantages should be included

Reply 1: Thank you for your comments. Additional information has been added to "3.10 Recent Advancements" section in lines 827-838.

Comment 2: Comparative Analysis:
The paper lacks data on the comparative effectiveness of available techniques that would provide the reader with valuable insights for clinical decision-making. A reflection of the available literature on topics such as margin positivity, cost-effectiveness, and patient-reported outcomes associated with each method would provide readers with valuable insights for clinical decision-making. Limitations of the literature on the above categories should be highlighted.
Reply 2: Added table 2 titled "Comparison of different localization techniques", with the parameters being positive margins, re-operation rate, cost per device, patient satisfaction.

Comment 3: Discussion of Patient Experience, Future direction
Mentioning studies that report on patient experience with the different techniques would be useful, if data on the topic are missing it should be reflected in the conclusion of the paper as an area of future research.
Reply 3: Davey MG, O'Donnell JPM, Boland MR, Ryan ÉJ, Walsh SR, Kerin MJ, Lowery AJ. Optimal localization strategies for non-palpable breast cancers –A network meta-analysis of randomized controlled trials. Breast (Edinburgh). 2022;62:103-13.

This meta-analysis contains information about the impact of localization techniques on patient satisfaction, therefore it is included in table 2.

Added in line 852-854 "3.11 future development" section.
"In addition, knowledge regarding patient-reported outcomes and cosmetic outcomes of different localization methods are still inadequate, therefore future studies in this area would be useful."

Comment 4: Conclusion:
The conclusion should include current gaps in knowledge (as described above) and highlight areas of future research.
Reply 4: "Future studies that report on patient experience and cosmetic outcomes with different localization techniques would be useful. In addition, the benefits of using biopsy markers, e.g. hydrogel markers, on subsequent surgical outcomes, especially margin status and re-excision rates, is not well documented in the literature, therefore more research on biopsy markers would be needed. Furthermore, an area of future research would be on integration of augmented reality in localization of non-palpable breast lesions." In lines 875 – 882.

Reviewer C
Comment 1: This article seems very interesting to me, as breast surgeons need evidence to determine the best method for detecting non-palpable lesions in breast cancer.

The latest Cochrane review is outdated (2015) and concludes that there is not enough evidence to recommend one method over another, and that more studies are needed.
Chan BK, Wiseberg-Firtell JA, Jois RH, et al. Localization techniques for guided surgical excision of non-palpable breast lesions. Cochrane Database Syst Rev 2015;2015

In recent years, several articles and meta-analyses shed light on this issue.
Davey MG, et al. Optimal localization strategies for non-palpable breast cancers –A network meta-analysis of randomized controlled trials. Breast 2022;62:103-13.
Banys-Paluchowski M et al. Intraoperative Ultrasound-Guided Excision of Non-Palpable and Palpable Breast Cancer: Systematic Review and Meta-Analysis. Ultraschall Med 2022;43:367-79.

However, I have several comments and questions regarding the manuscript:

Comment 1: Line 79-80: I would add that research comparing the different techniques among themselves is necessary, not just with the wire as the reference technique.
Reply 1: Thank you so much for your extensive and detailed comments. This suggestion is added in the conclusion in line 874-876.

Comment 2: Line 89: I would appreciate a more updated reference.
Reply 2: line 75. Thank you for the comment, 2020 is the most updated reference for world cancer statistics, according to both World Cancer Research Fund International and Global Cancer Observatory.

Comment 3: Line 123 - 124: I would appreciate a bibliographic citation.
Reply 3: Added in line 154-155

elzohery Yh, Gomaa MM, Mohamed G, Fadlalla WM, Taha SN, Ibraheem MH. Comparison of wire-guided localization in localization of non-palpable breast lesions. World journal of surgical oncology. 2023;21(1).

Park-Simon T-W, Müller V, Jackisch C, Albert U-S, Banys-Paluchowski M, Bauerfeind I, et al. Arbeitsgemeinschaft Gynäkologische Onkologie Recommendations for the Diagnosis and Treatment of Patients with Early Breast Cancer: Update 2023. Breast care (Basel, Switzerland). 2023;18(4):288-304.

Comment 4: Lines 126-128: Requires a bibliographic reference.
Reply 4: Added in line 160

Banys-Paluchowski M, Kuhn T, Masannat Y, Rubio I, de Boniface J, Ditsch N, et al. Localization Techniques for Non-Palpable Breast Lesions: Current Status, Knowledge Gaps, and Rationale for the MELODY Study (EUBREAST-4/iBRA-NET, NCT

05559411). Cancers (Basel). 2023;15(4).

Comment 5: Lines 146-147: A bibliographic reference is required.
Reply 5: Added in line 169

Civil YA, Duvivier KM, Perin P, Baan AH, van der Velde S. Optimization of Wire-guided Technique With Bracketing Reduces Resection Volumes in Breast-conserving Surgery for Early Breast Cancer. Clin Breast Cancer. 2020;20(6):e749-e56.

Comment 6: Line 168: There are other disadvantages of the WGL that the authors do not mention, and I consider them important, as they are widely described in the literature. They are as follows:

• It may require the use of more than one or two wires, increasing the patient's discomfort and surgical difficulty.
• It involves additional radiation for the patient, as the placement of the wire needs to be verified.
• It is highly dependent on the experience of the radiologist.
• There is ample literature that concludes that the WGL results in excessive excision of healthy tissue, removing large volumes without achieving improved margins in breast cancer-conserving surgery.
• As for the cost, it is true that it is an economical technique compared to others, but nonetheless, one must take into account the cost of the wire material in addition to the cost of radiological techniques (mammography, ultrasound, or MRI) and the increased cost in hospitalization time and in surgical time, as radiological verification of the surgical specimen is required (and the operating room minute cost is not negligible). See the following reference: Haloua MH, Krekel NMA, Coupé VMH, Bosmans JE, Lopes Cardozo AMF, Meijer S, et al. Ultrasound-guided surgery for palpable breast cancer is cost-saving: Results of a cost- benefit analysis. Breast. 2013;22(3).
Reply 6: Added these points to "3.2.2 limitations of WGL" section

Comment 7: Line 182: I would add some other advantages of ultrasound:
• It is a direct visualization technique performed by the same surgeon, so it doesn't depend on other specialists.
• Enables real-time visualization of the lesion, its size, depth, and margin assessment.
• It is not painful or uncomfortable for the patient.
• It allows for savings in hospital and surgical time since no devices need to be placed before surgery, and there's no need for post-operative specimen verification through radiology. This also results in a significant reduction in costs.
• It doesn't involve the handling of radioactive materials or additional radiation for the patient.
• Numerous studies have concluded that IOUS achieves smaller surgical specimen volumes, removing less healthy tissue without affecting margins, resulting in more precise surgery and improved cosmetic outcomes.

• It allows flexibility in the surgical schedule.
• I recommend that the authors review and add the following bibliography:

- Banys-Paluchowski M et al. Intraoperative Ultrasound-Guided Excision of Non-Palpable and Palpable Breast Cancer: Systematic Review and Meta-analysis. Ultraschall Med 2022;43:367-79
Reply: IOUS is a safe non-invasive technique for the localization of sonographically visible tumors that significantly improves margin rates in breast cancer
- Argacha P, Cortadellas T et al. Comparison of ultrasound-guided surgery and radio-guided occult lesions localization (ROLL) for nonpalpable breast cancer excision. Gland Surg 2023;12(9):1233-1241.
Reply: conclusion
IOUS in BCS for nonpalpable invasive breast cancer is more accurate than ROLL because it decreases excision volumes with the same rate of free margins and re-excision. Also, IOUS is a more efficient and comfortable technique, and just as safe as ROLL.
- Volders JH, Haloua MH, Krekel NM, et al. Current status of ultrasound-guided surgery in the treatment of breast cancer. World J Clin Oncol 2016;7:44-53.
Reply: The best evidence available demonstrates the benefits of IOUS with a significantly high proportion of negative margins compared with other localization techniques in palpable and non-palpable breast cancer. Additionally, IOUS is non-invasive, easy to learn, and can centralize the tumor in the excised specimen with a low amount of healthy breast tissue being excised. This could lead to better cosmetic results of BCS.
- Hoffmann J, Marx M, Hengstmann A, et al. Ultrasound-Assisted Tumor Surgery in Breast Cancer - A Prospective, Randomized, Single-Center Study (MAC 001). Ultraschall Med 2019;40:326-32.
Reply: Ultrasound-assisted breast surgery significantly increases the possibility of tumor-free margins and therefore reduces the risk of reoperations.
- Colakovic N, Zdravkovic D, Skuric Z, et al. Intraoperative ultrasound in breast cancer surgery-from localization of non-palpable tumors to objectively measurable excision. World J Surg Oncol 2018;16:184.
Reply: Over time, the use of IOUS has been transformed from being the means of localizing non-palpable lesions to an instrument yielding a reduced number of positive resection margins, with a smaller volume of healthy breast tissue excited around the tumor, by making the excision of the tumor optimal and objectively measurable.
Reply 7: Added these points and the references to “3.3 Intraoperative Ultrasound Localization” and “3.3.1 Advantages of IOUS” section

Comment 8: Line 185: For non-ultrasound-visible lesions, we can perform IOUS with echo-visible markers like hydrogel clips (see the next section).
Reply 8: Added this sentence to “3.3.2 Limitations of IOUS” section

Comment 9: Line 185: The authors do not mention the main limitation of IOUS, which

is that the technique requires training and has a learning curve, and is operator dependent.
Esgueva A, Rodríguez-Revuelto R, Espinosa-Bravo M, et al. Learning curves in intraoperative ultrasound-guided surgery in breast cancer based on complete breast cancer excision and no need for second surgeries. Eur J Surg Oncol 2019;45:578-83.
Another drawback is that it requires having an ultrasound machine in the operating room.
Reply 9: Added the points and reference to “3.3.2 Limitations of IOUS” section

Comment 10: Line 186-188: I don't think it makes sense to mention the mammographic guidance in this section where the ultrasound procedure is being explained, they are unrelated, and this concept is already mentioned in lines 197-199.
Reply 10: Removed mammographic guidance from this section

Comment 11: Line 190: Requires a bibliographic reference.
Reply 11: Added reference line 279

Guirguis MS, Adrada BE, Scoggins ME, Moseley TW, Dryden MJ, Le-Petross HC, et al. The Challenging Image-Guided Preoperative Breast Localization: A Modality-Based Approach. American journal of roentgenology (1976). 2022;218(3):423-34.
Comment 12: Line 226: The authors can correct this sentence by generalizing it: “Hydrogel clips (e.g., HydroMARK and others)”, as there is more than one brand marketed."
Reply 12: Line 432. Corrected to “A later generation consists of an additional hydrogel body surrounding the marker: Hydrogel clips (eg. HydroMARK® and others)”

Comment 13: Line 228: It would be important to add how long the hydrogel clip is visible on ultrasound.
Reply 13: Hydrogel clip visibility can last up to 12 months (line 439).

Comment 14: Line 282- 285: As advantages of ROLL, I would emphasize that it is a safe and effective technique, widely studied, and does not require external devices. Furthermore, its greatest advantage is that it allows for the localization of the sentinel lymph node with the same radiotracer.
I would add the advantage of the small size of the Iodine seed (4.5 mm).
Reply 14: Added to “3.6.1 advantages of radioactive techniques” section. Included an additional reference.

Ratnagobal S, Taylor D, Bourke AG, Kessell M, Madeley C, Robert MC, et al. Localisation accuracy with iodine-125 seed versus wire guidance for breast cancer surgery. Journal of Medical Radiation Sciences. 2023;70(3):218-28.

Comment 15: Line 287-292: In terms of disadvantages: surgical flexibility could be

considered more of a disadvantage for ROLL since it is necessary to inject the tracer hours or even days before the surgery. Additionally, I would add the high cost of both the ROLL procedure and the seed, as they are the most expensive. Also, it should be noted that it is not reversible, and it serves as an auditory guide rather than a visual one.
Reply 15: Added to "3.6.2 limitations of radioactive techniques" section

Comment 16: Line 329: I would add the advantage of the small size of the magnetic seed (5 mm).
Line 337: The cause should be better explained, as it is the main disadvantage of the magnetic seed: since it does not allow for the assessment of the response to neoadjuvant treatment by MRI.
Reply 16: Edited "3.7.2 limitations of magnetic techniques" section with the recommendations above.

Comment 17: Line 386: I wanted to add additional information about the limitations of radar techniques. Besides the cost, which is its main limitation, it's also important to consider its large size (the radar device is the largest of all the devices, measuring 12mm). This can be an advantage in terms of direct visualization and easy detection but a disadvantage in terms of more challenging placement, especially in the axilla or in small breast lesions. The larger size may also lead to more complications, such as hematomas.

Reply 17: Added in "3.8.2 limitations of radar techniques" section

Comment 18: Line 411-418: I agree with the authors that the main advantage of radiofrequency is its low cost compared to other techniques and the ease of handling the probe due to its small and manageable size. It is also important to emphasize that it is a device that does not migrate and is very useful for marking axillary lymph nodes.
Reply 18: In line 779, I added that the RFID tags do not migrate, therefore they are very useful for marking axillary lymph nodes.

Lowes S, El Tahir S, Koo S, Amonkar S, Leaver A, Milligan R. Pre-operative localization of axillary lymph nodes using radiofrequency identification (RFID) tags: a feasibility assessment in 75 cases. Clin Radiol. 2023;78(9):e668-e75.

Comment 19: Line 426: I would add as a disadvantage that its size is large (10mm), although it is smaller than the radar.
Reply 19: Added this in line 798, the size of the Localizer is 11cm long.

Comment 20: Line 454: I would add that more studies are needed to compare these techniques in terms of effectiveness, ease of use, patient comfort, cost, and the ability to achieve smaller volumes with optimal safety margins for improved aesthetic results and oncological safety.
Reply 20: Added table 2 titled "comparison of different localization techniques", with

the parameters being positive margins, re-operation rate, cost per device, and patient satisfaction.

Reviewer D

Comment 1: The manuscript is well organized. The following features could be better highlighted:

1) what is the criterion for defining oncological radicality in different articles?

Reply: oncological radicality means obtaining tumor-free margins and minimizing the risk of local recurrence, while optimal aesthetic outcomes require the preservation of an adequate and harmonious shape of the breast, which should always be symmetrical to the contralateral one, removing as little as possible

Reply 1:

Thank you for your comments.

Shirazi S, Hajiesmaeili H, Khosla M, Taj S, Sircar T, Vidya R. Comparison of Wire and Non-Wire Localisation Techniques in Breast Cancer Surgery: A Review of the Literature with Pooled Analysis. Medicina (Kaunas). 2023;59(7).

- Positive margin, re-excision rate

Banys-Paluchowski M, Kuhn T, Masannat Y, Rubio I, de Boniface J, Ditsch N, et al. Localization Techniques for Non-Palpable Breast Lesions: Current Status, Knowledge Gaps, and Rationale for the MELODY Study (EUBREAST-4/iBRA-NET, NCT 05559411). Cancers (Basel). 2023;15(4).

- Successful excision, Positive margin, re-excision rate

Davey MG, O'Donnell JPM, Boland MR, Ryan ÉJ, Walsh SR, Kerin MJ, Lowery AJ. Optimal localization strategies for non-palpable breast cancers –A network meta-analysis of randomized controlled trials. Breast (Edinburgh). 2022;62:103-13.

- Margin positivity, re-operation rates

Parisi S, Gambardella C, Conzo G, Ruggiero R, Tolone S, Lucido FS, et al. Advanced Localization Technique for Non-Palpable Breast Cancer: Radiofrequency alone VS Combined Technique with Ultrasound. Journal of clinical medicine. 2023;12(15):5076.

- According to Saint Gallen's recommendation in 2015, when the cancer margin was not inked at microscopical observation, the surgical radicality was obtained and reported as R0 surgery on the pathological report.

Positive margins were defined differently across studies, but a well-used definition is having ink on tumor. Since "no ink on tumour" was a consensus reached for negative surgical margins.

Comment 2: you didn't mention the combined technique RFID and US (Advanced Localization Technique for Non-Palpable Breast Cancer: Radiofrequency alone VS Combined Technique with Ultrasound. J Clin Med. 2023 Aug 2;12(15):5076. doi: 10.3390/jcm12155076). It could be added.

Reply 2: Thank you for your comment, the combined technique is added in line 784-785

Comment 3: can you focus better on which are the more mini-invasive approaches and re-operation rates?

Reply 3: Table 2, titled " comparison of different localization techniques" was added, with one of the parameters being re-operation rates

Reviewer E

Comment 1: The first request in Pubmed gave me the paper titled "Localization Techniques for Non-Palpable Breast Lesions: Current Status, Knowledge Gaps, and Rationale for the MELODY Study" (PMID: 36831516), which makes the need for this review questionable.

Reply 1: Thank you for your comments. This review provides more up-to-date information regarding the latest literature and in greater depth, is worthy to consider publishing at your prestige journal.

Comment 2: Besides, the review is incomplete and misses an in-depth overview of medical imaging modalities used for imaging markers. Although, the authors mentioned MRI, US, and CT, PET CT they omitted US-based techniques such as Doppler imaging, elastography, and contrast-enhanced US.

Reply 2: A section titled "3.1 overviews of imaging modalities used" is added in line 109, and it mentions US-based techniques Doppler imaging, elastography and contrast-enhanced US.

Comment 3: The main focus of the review is unclear. Do the authors review the modalities for pre-operative surgical planning, peri-operative surgical guidance, or image intervention guidance?

Reply 3: The main focus of the review is on the different techniques to localize non-palpable breast lesions and subsequently excise during breast-conserving surgery. Most of the techniques require pre-operative surgical planning, which includes the insertion of wire, marker, seed, reflector, or tag. Perioperative surgical and radiological guidance is also mentioned since it is related to the application of the localization techniques.

Comment 4: The manuscript is poorly structured. There is no clear section about imaging modalities, they are sometimes mentioned in the context of marker detection. The Introduction is very brief and reminds me more of an abstract.

Reply 4: Added a section titled "3.1 overviews of imaging modalities used"

Comment 5: The graphical material is insufficient. The authors provide only pictures of imaging markers and some devices, while it is essential to show the reader how the markers look in imaging modalities.

Reply 5: Added.

Reviewer F
Comment 1: Overall, well-written article. It does require more data within the body of the manuscript to provide evidence that one method of localization trumps the other.
For most articles that involve a literature review, it would also be useful for readers to know how many articles were identified and how many were both included and excluded, i.e. reasons for exclusion, etc.

I have also included comments within the attached manuscript for your reference.

Reply 1: Thank you for your comments. More updated data have been added to the body of the manuscript and table 2 titled “Comparison of different localization techniques” was added. It includes the parameters: positive margins, re-operation rate, cost per device and patient satisfaction.

The reply to the comments are attached in the separate PDF titled “Reviewer F's comments 20231223”.